

# Exhibit B

# Pharmacokinetics

SECOND EDITION, REVISED AND EXPANDED

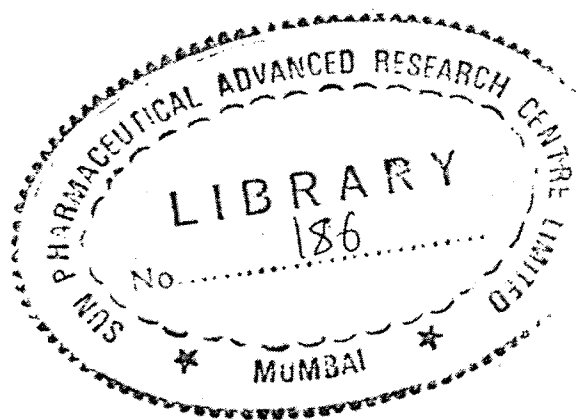
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Determination of  $C_{\max}$  and  $t_{\max}$ 

Mathematical relationships can be developed to estimate the time at which a peak plasma concentration of drug should be observed and the maximum plasma concentration at this time following first-order input into the body. Expanding Eq. (1.94) yields

$$C = \frac{k_a F X_0}{V(k_a - K)} e^{-Kt} - \frac{k_a F X_0}{V(k_a - K)} e^{-k_a t} \quad (1.102)$$

which when differentiated with respect to time gives

$$\frac{dC}{dt} = \frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t} - \frac{k_a K F X_0}{V(k_a - K)} e^{-Kt} \quad (1.103)$$

When the plasma concentration reaches a maximum ( $C_{\max}$ ) at time  $t_{\max}$ ,  $dC/dt = 0$ . Therefore,

$$\frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t_{\max}} = \frac{k_a K F X_0}{V(k_a - K)} e^{-K t_{\max}} \quad (1.104)$$

which reduces to

$$\frac{k_a}{K} = \frac{e^{-K t_{\max}}}{e^{-k_a t_{\max}}} \quad (1.105)$$

Taking the logarithm of both sides of Eq. (1.105) and solving for  $t_{\max}$  yields

$$t_{\max} = \frac{2.303}{k_a - K} \log \frac{k_a}{K} \quad (1.106)$$

For a given drug, as the absorption rate constant increases, the time required for the maximum plasma concentration to be reached decreases.

The maximum plasma concentration is described by substituting  $t_{\max}$  for  $t$  in Eq. (1.94):

$$C_{\max} = \frac{k_a F X_0}{V(k_a - K)} (e^{-K t_{\max}} - e^{-k_a t_{\max}}) \quad (1.107)$$

However, a simpler expression can be obtained. From (1.105) it can be shown that

$$e^{-k_a t_{\max}} = \frac{K}{k_a} e^{-K t_{\max}} \quad (1.108)$$

Substituting for  $e^{-k_a t_{\max}}$ , according to (1.108), in (1.107) yields

$$C_{\max} = \frac{k_a F X_0}{V(k_a - K)} \frac{k_a - K}{k_a} e^{-K t_{\max}} \quad (1.109)$$

which is readily simplified to

$$C_{\max} = \frac{F X_0}{V} e^{-K t_{\max}} \quad (1.110)$$

The values of  $C_{\max}$  and  $t_{\max}$  under the special circumstance when  $k_a = K$  is of mathematical interest and will be considered briefly. Under these conditions, Eq. (1.92) can be written as

$$\bar{X} = \frac{K F X_0}{(s + K)^2} \quad (1.111)$$

Hence

$$X = K F X_0 t e^{-K t} \quad (1.112)$$

$$C = \frac{K F X_0 t e^{-K t}}{V} \quad (1.113)$$

and

$$\log C = \log \frac{K F X_0 t}{V} - \frac{K t}{2.303} \quad (1.114)$$

Equation (1.114) indicates that when  $k_a = K$ , a semilogarithmic plot of  $C$  versus  $t$  will contain no linear segments.

Differentiating Eq. (1.113) with respect to time yields

$$\frac{dC}{dt} = \frac{K F X_0}{V} e^{-K t} - \frac{K^2 F X_0}{V} t e^{-K t} \quad (1.115)$$

At  $t_{\max}$ ,  $C = C_{\max}$  and  $dC/dt = 0$ . Therefore,

$$\frac{K F X_0}{V} e^{-K t_{\max}} = \frac{K^2 F X_0}{V} t_{\max} e^{-K t_{\max}} \quad (1.116)$$